

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 78N–0227; DESI 11853]

Trimethobenzamide Hydrochloride Injection and Capsules; Drug Efficacy Study Implementation; Final Evaluation

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) announces the resolution of issues concerning trimethobenzamide hydrochloride injection and capsules. This notice announces the approval of a supplemental new drug application (NDA) for Tigan (trimethobenzamide hydrochloride) Capsules, 300 milligrams (mg), and states that continued marketing of unapproved trimethobenzamide hydrochloride injection and capsule products is unlawful and is subject to FDA regulatory action.

ADDRESSES: Requests for FDA’s opinion on whether a supplement to an abbreviated new drug application (ANDA) is required for a specific trimethobenzamide hydrochloride injection product should be identified with Docket No. 78N–0227 and reference number DESI 11853 and be directed to the Office of Generic Drugs (HFD–600), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., rm. 150, Rockville, MD 20855–2773. Requests for an opinion on the applicability of this notice to a specific trimethobenzamide hydrochloride injection or capsule product should be identified with Docket No. 78N–0227 and reference number DESI 11853 and directed to the Division of Prescription Drug Compliance and

Surveillance (HFD-330), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855.

FOR FURTHER INFORMATION CONTACT: Brian L. Pendleton, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION:

I. Background

As part of its Drug Efficacy Study Implementation (DESI) program, in a notice published in the **Federal Register** of February 24, 1971 (36 FR 3435) (the 1971 notice), FDA announced its conclusion that certain drug products containing trimethobenzamide hydrochloride were: (1) Probably effective for nausea and vomiting due to radiation therapy or travel sickness and for emesis associated with operative procedures, labyrinthitis, or Meniere's syndrome; (2) lacking substantial evidence of effectiveness for the treatment of nausea and vomiting due to infections, underlying disease processes, or drug administration; and (3) possibly effective for all other labeled indications. The 1971 notice listed three trimethobenzamide hydrochloride products: Tigan Solution for Injection (NDA 11-853), Tigan Capsules (NDA 11-854), and Tigan Suppositories (NDA 11-855). Roche Laboratories held the NDAs for these three products.

In the **Federal Register** of January 9, 1979 (44 FR 2017) (the 1979 notice), FDA published a notice announcing that the agency was reclassifying trimethobenzamide hydrochloride injection and capsules to effective for certain indications and to lacking substantial evidence of effectiveness for their other (previously designated) less-than-effective indications. Specifically, FDA

concluded that trimethobenzamide hydrochloride injection and capsules are effective for the treatment of postoperative nausea and vomiting and for nausea associated with gastroenteritis. The agency also concluded that trimethobenzamide hydrochloride injection and capsules lack substantial evidence of effectiveness for their other labeled indications. (In the same issue of the **Federal Register** (44 FR 2021), FDA published a notice reclassifying trimethobenzamide hydrochloride suppositories to lacking substantial evidence of effectiveness and proposed to withdraw approval of NDAs for trimethobenzamide hydrochloride suppositories.)

The 1979 notice stated that two NDAs for trimethobenzamide hydrochloride injection and capsules not included in the February 1971 notice were affected by the new notice: NDA 17-530, for Tigan Injection, and NDA 17-531, for Tigan Capsules, both held by Beecham Laboratories (Beecham) (44 FR 2017 at 2018). The 1979 notice stated that, according to bioavailability studies submitted by Beecham, the relative bioavailability or extent of absorption of a 250-mg capsule was 56-62 percent of that of the 200-mg intramuscular injection. Based on these studies, FDA concluded that the oral dose of trimethobenzamide hydrochloride should be approximately two times the intramuscular dose. FDA noted that on May 2, 1978, Beecham supplemented its NDA for Tigan Capsules to reformulate the capsule dosage form from 100 mg and 250 mg to 200 mg and 400 mg, respectively. The agency stated that the reformulated products were being handled through the normal supplemental NDA procedures (44 FR 2017 at 2019).

FDA stated in the 1979 notice that the agency was prepared to approve ANDAs and abbreviated supplements to previously approved NDAs for trimethobenzamide hydrochloride injection and capsules under certain

conditions pertaining to the form of the drug (i.e., the drug product was in sterile aqueous solution suitable for intramuscular administration or in capsule form suitable for oral administration) and in its labeling. Labeling was to state, among other things, that the drug was indicated for the treatment of postoperative nausea and vomiting and for nausea associated with gastroenteritis. The section on dosage and administration was to specify the following:

For the treatment of nausea secondary to gastroenteritis: 200 mg intramuscularly or 400 mg orally.

For the treatment of nausea and vomiting postoperatively: 200-mg intramuscular injection followed in 1 hour by a second 200-mg intramuscular injection, or 400 mg orally.

(44 FR 2017 at 2019)

The 1979 notice stated that the marketing of trimethobenzamide hydrochloride injection and capsule products that were the subject of an approved or effective NDA could be continued provided that, on or before March 12, 1979, the holder of the application submitted a supplement for revised labeling and a supplement to provide other specified information. In addition, for the capsule dosage form, each application holder was required to submit, by July 9, 1979, evidence demonstrating the in vivo bioavailability of the drug product by comparing the oral capsule product with Beecham's intramuscular injection and with an oral solution. The notice also stated that approval of an ANDA must be obtained prior to marketing other trimethobenzamide hydrochloride injection and capsule products (44 FR 2017 at 2019).

In the 1979 notice, FDA gave notice of an opportunity for a hearing to the holders of NDAs for trimethobenzamide hydrochloride injection and capsules, and to all other interested persons, that the agency proposed to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(e)) withdrawing approval of the NDAs and all amendments and supplements thereto providing for the indications determined by the agency to lack substantial evidence of effectiveness (44 FR 2017 at 2020). The agency stated that the notice of an opportunity for a hearing encompassed all issues relating to the legal status of the drug products subject to the notice, including identical, related, or similar drug products as defined in § 310.6 (21 CFR 310.6). In accordance with section 505 of the act and parts 310 and 314 (21 CFR parts 310 and 314), FDA gave the applicants and all other persons who manufacture or distribute a drug product that is identical, related, or similar to a drug product named in the notice an opportunity for a hearing to show why approval of the NDAs providing for the claims involved (i.e., those claims found to be lacking substantial evidence of effectiveness) should not be withdrawn, and an opportunity to raise, for administrative determination, all issues relating to the legal status of a named drug product and all identical, related, or similar drug products (44 FR 2017 at 2020).

The 1979 notice stated that the failure of an applicant or any other person subject to the notice to file a timely written appearance and request for a hearing as required by § 314.200 constituted an election by such person not to make use of the opportunity for a hearing and a waiver of any contentions concerning the legal status of any drug product subject to the notice. The notice further stated that any such drug product labeled for the indications lacking substantial evidence of effectiveness specified in the notice could not thereafter

lawfully be marketed, and the agency would initiate appropriate regulatory action to remove any such drug products from the market (44 FR 2017 at 2020).

In a letter dated January 30, 1979, Beecham requested a hearing on the proposed NDA withdrawals. In a letter dated March 5, 1979, Beecham submitted data in support of its request for a hearing. Beecham was the only party to request a hearing.

II. King Pharmaceuticals' Supplemental NDAs for Tigan Injection and Capsules

On November 12, 1999, King Pharmaceuticals, Inc. (King), purchased the NDAs for three Tigan (trimethobenzamide hydrochloride) products previously held by Beecham: NDA 17-530 (injection), NDA 17-531 (capsules), and NDA 17-529 (suppositories). FDA subsequently initiated discussions with King on bringing the Tigan products into compliance with the 1979 notices on trimethobenzamide hydrochloride drugs.

A. Supplemental NDA for Tigan Capsules

As a step toward resolution of the issues in the 1979 notice regarding trimethobenzamide hydrochloride injection and capsules, and pending resolution of Beecham's request for a hearing, in December 1999, FDA agreed to allow King to attempt to demonstrate that a 300-mg trimethobenzamide hydrochloride capsule product is bioequivalent to the 200-mg Tigan injection product. In a supplemental NDA dated February 8, 2001, and received by FDA on February 14, 2001, King requested approval of a 300-mg Tigan (trimethobenzamide hydrochloride) capsule product.

In an agreement that became effective on August 16, 2001 (the Agreement), FDA and King agreed to take several actions to resolve the matter of the

compliance of Tigan products with the 1979 notices. Among other things, King agreed to withdraw the request for a hearing (originally submitted by Beecham) on matters related to NDAs 17-529 (Tigan Suppositories), 17-530 (Tigan Injection), and 17-531 (Tigan Capsules), and all amendments and supplements thereto, within 10 days of the effective date of the Agreement. In a letter dated August 24, 2001, King withdrew its request for a hearing on these matters in accordance with the Agreement.

In a letter dated December 13, 2001, FDA approved King's supplemental NDA for 300-mg Tigan Capsules. The approval letter states that the supplemental NDA provides for the following in response to the 1979 notice classifying the drug as effective for postoperative nausea and vomiting and nausea associated with gastroenteritis: Draft labeling; results of bioavailability studies; and updated manufacturing, control, and testing procedures.

B. Supplemental NDA for Tigan Injection

In a letter dated December 19, 2001, King submitted a supplemental NDA, in accordance with the Agreement and § 314.70(c), to incorporate in NDA 17-530 (Tigan Injection) the new Tigan labeling approved by FDA on December 13, 2001, as part of the approval of King's supplemental NDA for Tigan Capsules. Among other things, the labeling states that Tigan is indicated for the treatment of postoperative nausea and vomiting and for nausea associated with gastroenteritis (the indication specified in the 1979 notice and in the recently-approved labeling for Tigan Capsules), and that the dosage of Tigan Capsules is 300 mg. Under § 314.70(c), the supplemental NDA for Tigan Injection did not require prior agency approval.

III. Marketing of Other Trimethobenzamide Hydrochloride Injection and Capsule Products

In light of King's withdrawal of its hearing requests, FDA's approval of 300-mg Tigan Capsules, and King's revision of the labeling for Tigan Injection, FDA is issuing this notice in final resolution of all matters in this proceeding involving trimethobenzamide hydrochloride injection and capsules. (At a later date, FDA intends to issue a notice resolving all matters in FDA Docket No. 78N-0224 (DESI 11853) involving trimethobenzamide hydrochloride suppositories.)

As stated above, no party other than Beecham submitted a request for a hearing in response to the 1979 notice. Therefore, all other parties waived any possible contentions regarding the legal status of their trimethobenzamide hydrochloride injection and capsule products (including those products listed in the 1971 notice).

Trimethobenzamide hydrochloride capsule products made by several different manufacturers are currently listed with FDA. Continued marketing of an unapproved trimethobenzamide hydrochloride capsule product is unlawful and is subject to regulatory action. Any person wishing to market a trimethobenzamide hydrochloride capsule product must submit and obtain FDA approval of a new NDA or ANDA.

With respect to trimethobenzamide hydrochloride injection, the FDA publication entitled "Approved Drug Products With Therapeutic Equivalence Evaluations" (the Orange Book), 22d ed. (2002), includes two products other than Tigan Injection on the "Prescription Drug Product List." Four trimethobenzamide hydrochloride injection products are on the Orange Book's "Discontinued Drug Product List." For some of these trimethobenzamide

hydrochloride injection products, an ANDA supplement to revise product labeling may be required for continued or renewed marketing. To determine whether an ANDA supplement is required for a particular product, write to the Office of Generic Drugs (see **ADDRESSES**).

Any drug product that is identical, related, or similar to the trimethobenzamide hydrochloride injection and capsule products named above, and is not the subject of an approved application, is covered by the applications named above (i.e., NDAs 17-530 and 17-531) and is subject to this notice (21 CFR 310.6). Any person who wishes to determine whether a specific product is covered by this notice should write to the Division of Prescription Drug Compliance and Surveillance (see **ADDRESSES**).

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 201(n), 502, 505, 52 Stat. 1041, 1050–1053), as amended (21 U.S.C. 321(n), 352, 355), and under the authority delegated to the Director of the Center for Drug Evaluation and Research (21 CFR 5.100).

Dated: December 18, 2002.

Janet Woodcock,

Director, Center for Drug Evaluation and Research.

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